

Percutaneous Left Atrial Appendage Exclusion Therapy: Who, Why and How?

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Abstract

Purpose: Patients with atrial fibrillation are at an increased risk of having a cardio embolic stroke. Stroke is a leading cause of death and disability worldwide. Current guidelines recommend an antithrombotic regimen to prevent thromboembolism in medium and high risk patients with AF. However, a substantial number of patients are not eligible for this therapy. The exclusion of the left atrial appendage (LAA) from circulation seems to be an alternative strategy for stroke prevention in AF. This review focuses on the different strategies for LAA exclusion with special focus on the WATCHMAN Device.

Two devices are currently in use for percutaneous transcatheter occlusion of the LAA: the WATCHMAN® - device and the AMPLATZER® –septal occluder. For both devices safety and feasibility data are available.

Additionally about 200 patients received a PLAATO® –device- which is currently no more available due to economic reasons. Patients treated with the PLAATO device were at high risk for thromboembolic stroke and had contraindications for oral anticoagulation therapy. The Watchman® -device was implanted in 800 patients that were eligible for long-term anticoagulation therapy with a moderate risk for thromboembolic stroke due to non-valvular AF.

Summary: For both devices, a reduction in the risk of stroke was documented and device implantation was shown to be safe and feasible. Provided the ongoing trials show noninferiority to oral anticoagulation, another therapeutic option will become available to prevent ischemic strokes.

Introduction

Incidence und Prevalence

Stroke is a leading cause of death and disability worldwide. About 15- 20% of ischemic strokes have a cardio embolic origin. Atrial fibrillation (AF)

affects 3-5% of the population older than 65 years and is the most common arrhythmia of clinical relevance. With an aging population, the prevalence is likely to increase 2.5 fold over the next 50 years.¹

The incidence of atrial fibrillation increases with

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Table 1 CHADS₂ * Risk Score

Risk factor	CHADS ₂ Score
Congestive heart failure (LVEF >35%)	1
History of hypertension	1
Age > 75 years	1
Diabetes mellitus	1
Stroke or TIA (prior)	2

* CHADS₂ is an acronym derived from the initial letter from the risk factors and the scoring 2 for prior stroke or TIA. The Score is calculated by the scores of the present risk factors.

age from about 2 % in patients aged 60-69 years to approximately 8% in patients older than 79 years.²

Additionally several risk factors have been described as markers for an increased risk for thromboembolism. The CHADS₂ stroke risk index was developed to estimate the stroke rate in AF patients [Table 1]. The higher the score, the higher the risk of stroke.³ [Table 2]

The current guidelines for therapy of AF recommend an antithrombotic regimen with warfarin as a class 1A indication to prevent thromboembolism in all patients with AF with a CHADS₂ score of >1, except for those with contraindications.⁴ Without anticoagulant therapy the risk of stroke is about 5 % per year in patients < 65 years and it increases to over 8% per year in patients over 75.⁵ The effectiveness of an anticoagulation therapy to prevent ischemic strokes related to atrial fibrillation was demonstrated in several studies. One of the largest studies- the SPAF – I- trial-demonstrated a risk reduction of about 67% with warfarin as compared with placebo.⁶ Studies assigned the effects of warfarin as compared with aspirin, clopidogrel or a combination of both but none of them were able to show a superiority of one of these therapies over warfarin.^{6,7}

Unfortunately less than half of all patients, who have an indication for anticoagulation therapy, receive warfarin therapy for various reasons.^{9,10} Additionally warfarin therapy is related to many disadvantages such as the narrow therapeutic range, the potential risk of severe bleedings, the need for a close monitoring and the pharmacological interactions as well as the influence by diet, herbal supplements or concomitant diseases. The discontinuation rate for those under therapy is estimated to be 38 % per year approximately¹¹

Therefore many activities are focused on the development of novel therapeutic tools to prevent AF related strokes. Besides new medication, one development that might be promising is the interventional exclusion of the left atrial appendage (LAA) from circulation.

The Left Atrial Appendage as the target

Ischemic strokes associated with atrial fibrillation are caused by secondary embolisation of thrombi from the left atrial appendage (LAA) in 91% to 98 %.¹² The pathophysiology of thromboembolism in patients with AF is uncertain. Although Virchow postulated stasis, hypercoagulation and endothelial dysfunction as the mechanisms leading to thrombus formation, the pathophysiology of thromboembolism in atrial fibrillation remains uncertain.⁴

The impaired mechanical contraction of the left atrium and especially the LAA in patients with AF leads to a reduced blood flow velocity and is supposed to result in spontaneous echo contrast, thrombus formation, and embolic events.¹³⁻¹⁸ In addition, the morphology of the LAA might have an impact on the risk of thrombus formation. The LAA is usually a long, tubular, hooked structure with a large variability in morphology. Its size ranges from 20 to 45 mm in length and 15 to 35 mm in orifice diameter.¹⁹ In atrial fibrillation LAA casts at necropsy had a higher volume, larger orifices, and fewer branches and were broader than those of patients with sinus rhythm.²⁰ Functionally, the LAA plays a role as a “decompression” chamber, besides the production of atrial natriuretic peptide. Several studies suggest that the LAA is more distensible than the left atrium.

The Exclusion of the LAA from Circulation as an Alternative Therapy to Warfarin for Thrombus Prevention

For more than half a century physicians try to ex-

Table 2 Classification of risk groups through the CHADS₂ Score

Risk factor	CHADS ₂ Score
Low risk	0-1
Intermediate risk	2-3
High risk	>4

clude the LAA from circulation in patients with AF for thromboembolic prophylaxis. Even in the pre-warfarin era 1946 the surgical amputation of the LAA was described in two patients for prevention of thromboembolic events.²⁴ This procedure of LAA obliteration/ amputation has been performed first in patients undergoing mitral valve surgery or maze procedure. In this setting the results of LAA exclusion were inconclusive. In 2003 Garcia – Fernandez reported about a series of 58 patients, in whom ligation of the LAA was performed during mitral valve surgery. He reported about incomplete sealing of the LAA in a transesophageal echo follow up of about 10 % of patients. In these patients the risk of late embolism was significantly increased with an odds ratio of 6.7.²² On the other hand, a recently published prospective study by Almahameed et al. could show that also in patients after LAA exclusion the rate of thromboembolism was 15 % in those without postoperative warfarin therapy and 10% in those patients with postoperative warfarin therapy after 3.6 years of follow up.³⁴

In patients undergoing other cardiac surgery than mitral valve surgery, the amount of available data is limited. First data of the Left Atrial Appendage Occlusion Study-[LAAOS] pilot trial in patients undergoing coronary artery bypass surgery (77 patients) showed that the procedure of LAA occlusion is safe and does not prolong overall length of surgery. However, the benefit of a surgical LAA occlusion/ amputation, with respect to mortality and morbidity, is unknown so far, as the study is still ongoing with a planned inclusion rate of 2500 patients.²³

Given the fact that several studies report an incomplete occlusion of the LAA after surgical ligation in a high percentage of patients underlines the need for further development of the technique.^{23, 24} Recently Salzberg and colleagues reported on a new LAA Clip [AtriCure Inc. West Chester, Ohio] that was successfully tested in animals. The clip provided a total exclusion of the LAA from circulation.²⁵ However, also nonsurgical, interventional devices that exclude the LAA from circulation have been

Figure 1: Watchman – Device and Watchman „shorty“



developed. Three different interventional devices have been described so far for transcatheter LAA occlusion:

- A) PLAATO® System- currently no longer commercially available
- B) Amplatzer septal occluder – commercially available but not approved for this indication
- C) WATCHMAN® Device – so far available only for studies, but FDA-approval expected for this year

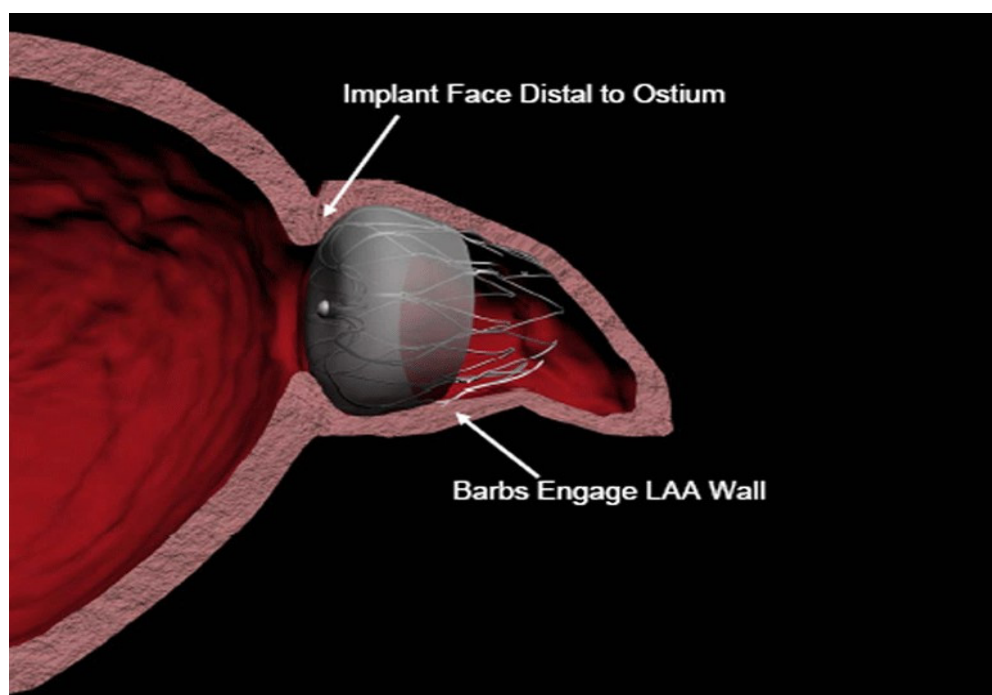
A) PLAATO® System

The PLAATO® System (originally produced by ev3 Inc., Plymouth, Minnesota, USA) consists of a self-expandable nitinol cage covered with a non-thrombogenic ePTFE membrane to exclude blood flow from the LAA. Different sizes (15-32mm) of the device were available, and a 14 French introducer sheath was required for implantation. Nakai et al. was the first to report on the Percutaneous LAA Transcatheter Occlusion (PLAATO®) - System. Feasibility and safety of this transseptal system was evaluated in 25 dogs.²⁶ The LAA could be occluded successfully in all 25 dogs safely and quickly. The sealing of the LAA seemed to be complete in all cases. Sievert et al published the first in man experience with the PLAATO® System. Fifteen patients with chronic atrial fibrillation

and contraindication for warfarin therapy were recruited for the study. In all patients the LAA could be successfully occluded. At 1 month follow up there were no complications or embolic events.²⁷

At present, more than 200 patients were treated with the PLAATO® device so far. 98% of patients could be successfully treated with minor complications. There was one device embolisation and 3% of patients developed pericardial effusions during/after the implantation procedure. One of these patients died due to cerebral hemorrhage after surgical pericardiocentesis.²² The study group analyzed a follow up of 250 patient years and documented an annual stroke rate of 3.2 % in patients having the PLAATO® device. The expected annual stroke risk according to the CHADS₂ Score was 6.5% under aspirin therapy in these individuals. One percent of the PLAATO® patients developed a flat thrombus attached to the surface of the device, which resolved under therapy with aspirin, clopidogrel and low molecular weight heparin. No mobile clots, mitral valve damage or pulmonary vein obstruction was observed. Therefore it was concluded that LAA occlusion with the PLAATO® device reduces the relative risk of stroke by 51%^{28, 22} Currently the device is no longer available, solely due to commer-

Figure 2: Schematic view of an implanted WATCHMAN Device



cial and not to medical reasons.

B) Amplatzer® septal occluder

The first and only study of left atrial appendage occlusion with the Amplatzer® septal occluder (AGA Medical Corp. Golden Valley, MN; USA) devices was published in 2003. The ease use of these devices in occluding patent foramen ovale or atrial septal defects lead to first experimental occlusion of LAA with these devices by Meier et al.³⁰

This first report included 16 patients that were treated in four centers with successful implantation in 15 patients. One acute device embolisation occurred. However, the device was surgically removed. At 4 months follow up, there were no further complications, the devices were stable in position and the LAA was completely occluded in all cases. Within this follow up period no thrombo-

embolic complications were reported. Nevertheless, for the Amplatzer ASD Occluder there are no further data available in LAA occlusion and large studies are lacking.

C) WATCHMAN® Device

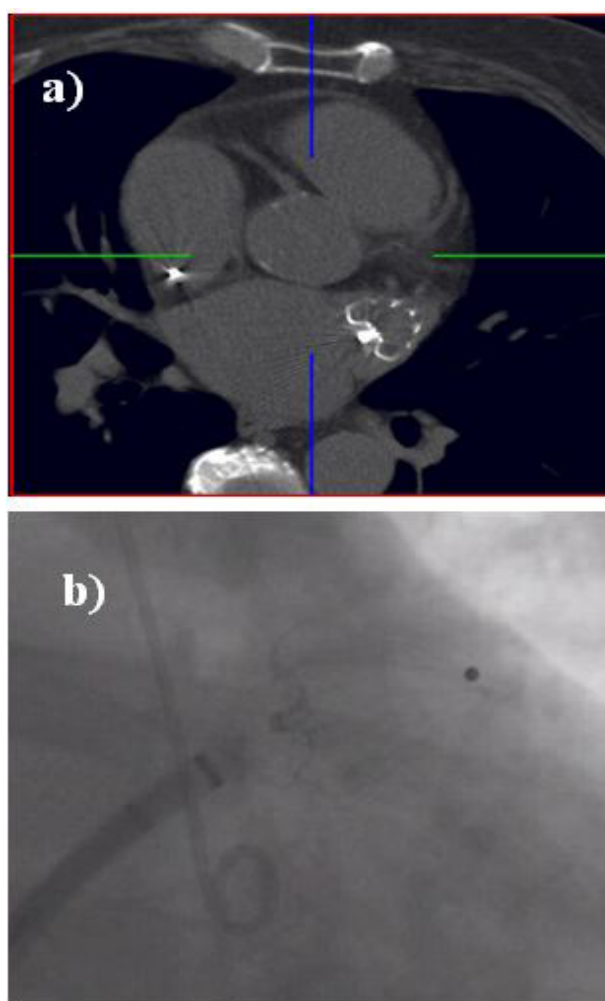
The Watchman ®- Left Atrial Appendage Occlusion Device (Atritech Inc., Plymouth, Minnesota, USA) is comprised of a self-expanding nitinol frame structure with fixation barbs and a permeable polyester fabric [Figure 1 and 2] that covers the left atrial facing surface of the device. Currently, the device is available in a size ranging from 21 to 33 mm. For WATCHMAN® device implantation, a transseptal access sheath (14 Fr) and a delivery catheter is necessary.

In a pilot trial 75 patients were included to asses safety and feasibility of the device. Patients had an

Figure 3: Implanted WATCHMAN Device

a) CT Scan: the device is in situ in the LAA

b) Fluoroscopy: The device was released in the LAA (arrow), the sheath is positioned in LA for fluoroscopic control (asterisk)



average CHADS₂ Score of 1.8 points corresponding to a moderate risk for stroke.³¹ Patients with impaired left ventricular function (< 35%), congenital heart disease, symptomatic carotid disease, prosthetic heart valves and significant neurological defects after prior stroke were excluded. The implantation procedure was performed under general anesthesia and TEE guidance. In 66 of the 75 patients (88 %) the device could be implanted successfully [Figure 3]. Implantation failure occurred in 9 patients due to unsuitable LAA anatomy (7 patients), core wire malfunction (1 patient) and impossible transseptal crossing (1 patient). Complications occurred in 5 of the first 16 patients treated with the first generation of the device. There were two embolisations of the device, one delivery system failure, one surgical device explantation after incorrect positioning, and one patient with transient air embolism.

Therefore, the device and the delivery system were modified after these first 16 patients. Fifty-three additional patients were implanted with the second-generation device and no further device embolization occurred. There was one significant pericardial effusion due to an overly vigorous tug test but no other relevant complications.³¹ After a mean follow up of 24 months there were no major strokes at all. Two deaths occurred during follow up period, which were not device related. In one patient, who died 9 months after device implantation due to a Type A aortic dissection, a complete endothelialisation of the Watchman device and the LAA was observed at autopsy. These data provide considerable evidence that implantation of the re-designed device is safe and feasible. Another randomized, prospective multicenter study (The WATCHMAN® Left Atrial Appendage System for Embolic PROTECTION in Patients With Atrial Fibrillation (PROTECT AF)- study), which is the first controlled trial in this field, compares Watchman device implantation with standard anticoagulation therapy. The recruitment period for this study ended in summer 2008.¹¹ The study included 800 patients at 39 centers in Europe and USA. The patients were randomized 2: 1 for device implantation vs. medical therapy only. All patients randomized in this study were eligible for standard warfarin therapy. For demonstration of non-inferiority of the WATCHMAN® device compared to warfarin therapy to reduce the incidence of stroke, 900 patient years of follow up were analyzed. The

data of this study will be published later in 2009 and are currently not yet available.

Summary and Conclusion

Patients with atrial fibrillation, especially in the older population, are at increased risk of stroke/TIA or PRIND, presumably because of stagnant blood flow within the left atrial appendage- a highly complex structure of the left atrium-, leading to thrombus formation. The annual risk of stroke in AF increases with age from about 5% in patients that are younger than 65 years to about 8 % at the age over 80. Besides age, cardiovascular diseases, hypertension, ischemic heart disease, congestive heart failure, valvular heart disease, and diabetes, have an impact on the prevalence of AF and also on the risk of stroke. The CHADS₂ score is a good validated score with a high correlation to the event rate.

Three therapeutic options exist to prevent ischemic strokes in those patients: The first and most popular is chronic anticoagulation therapy with warfarin, which is highly effective in preventing cardioembolic events and which is superior to other pharmacological approaches so far.³² However, oral anticoagulation is associated with several problems and significant risks: In about one third of patients this therapy is contraindicated,³¹ the rate of discontinuation of therapy is up to 38%/year¹² and there is a narrow therapeutic window with a potential risk of severe bleeding of about 2 % per year³⁴ Furthermore, less than half of all patients who are receiving anticoagulant treatment are within the therapeutic range with regard to INR.¹⁰ Therefore, new oral medication for anticoagulation without the risks and problems of vitamin K antagonists are under way and were tested at present in phase III- studies.

The second way for prevention of thromboembolism from the LAA is the exclusion of the LAA from circulation by surgical techniques. Regardless of the technique, first established in 1946, there are rare data available regarding the rates of successful LAA occlusion by various surgical techniques and in note of complications. In addition, it has never been shown that such an approach really reduces the incidence of stroke. Further studies with large patient populations and clinical endpoints are required to underline the effectiveness of these sur-

gical interventions. Also for a newly developed clip system (LAA Clip; AtriCure Inc. West Chester, Ohio, USA) there are only safety and feasibility data available in an animal model so far. First in man studies are expected and we have to await the issue.

But all these approaches are only for patients undergoing heart surgery for other reasons. In the last ten years, percutaneous occlusion systems were developed in order to seal the LAA in a less traumatic way as a third way to go for stroke prevention in AF patients. The periprocedural success rates are high for all the devices. However, the number of patients treated with such devices so far is small in relation to the population receiving warfarin and long term follow up data are lacking.

The first system specially developed for interventional LAA occlusion was the PLAATO®-System. The safety and feasibility of the system in humans was shown in patients with contraindication for chronic oral anticoagulation therapy. A risk reduction of about 50% for the incidence of ischemic strokes in this patient population was demonstrated after implantation of the device and chronic aspirin administration as compared with their statistically calculated risk. However, procedural complications like pericardial effusions/tamponade, device embolisation and device failure have been described in about 5% of patients.

The second system developed to occlude the LAA, is the WATCHMAN®-device. Implantation of the device was shown to be safe and feasible in a pilot trial in humans with atrial fibrillation. The patient population in this study had a lower risk for ischemic stroke with a CHADS² Score of 1.8 points as compared to 2.5 points in patients treated with the PLAATO®-device. Due to the permeable nature of the membrane of the WATCHMAN®-device (das war nicht der Grund, es war eine Bauchentscheidung, zunächst wegen Fremdkörper Antikoagulation fortzuführen, wegen Thrombenbildung auf Device in der Pilotstudie ASS und Clopidogrel bis 6 Monate, jetzt gibt es ha auch die ASAP-Studie, wo gänzlich auf Marcumar verzichtet wird) an oral anticoagulation after implantation procedure for 45 days and a double therapy with aspirin and clopidogrel for up to 6 months is required. The first generation of the device had a higher complication rate (device embolisation, device failure). After re-design of the WATCHMAN®-device these

complications were diminished, at presence stroke rate is 0% at 2 year follow up as compared with an anticipated stroke rate of 1.9% calculated with the CHADS² Score.

Data from the Protect AF Trial- (FDA approval trial) are under supervision and not yet published. The third interventional method, implantation of an Amplatzer septal occluder into the orifice of the LAA was shown only in a single center experience with few patients and a high rate of embolisations. Also with this method there are some short term results available, but the device is not approved for this indication and randomized data are lacking, therefore this method was left so far. The AGA-company is also on the way with a special designed device for LAA closure, but it is not yet commercially available and there are no data in the literature so far about this device.

Conclusions

LAA occlusion with the WATCHMAN®-device, with the Amplatzer® septal occluder as well as with the PLAATO® Occluder are safe and feasible. At present only the Amplatzer septal occluder and the WATCHMAN® occluder are (partially) available. No device is approved by the FDA with the indication occlusion of the LAA in patients with AF, but both devices are CE marked. At present the WATCHMAN technology was submitted to the FDA for assessment and the FDA approval is expected for 2009. Because of the growing prevalence of AF especially in the elderly, in whom anticoagulation carries a high risk or is contraindicated, this device may offer an attractive solution to prevent atrial fibrillation-related thromboembolic events. Nevertheless, both, the PLAATO® and the WATCHMAN®-device, demonstrated that there is a measurable risk in implanting such new devices with an investigators learning curve at the beginning. Provided the PROTECT –AF trial shows non-inferiority to oral anticoagulation with warfarin, another therapeutic option will become available to prevent ischemic strokes.

On the other hand, newly developed drugs like oral Factor Xa Inhibitors like rivaroxaban (Bayer Health Care; Leverkusen Germany); DU-176 b (Daichi-Sankyo Ltd. Tokyo Japan) or Dabigatran (Boehringer Ingelheim GmbH; Ingelheim, Germany) may play an increasing role in the therapy of

AF in the future with much less risk for bleeding and a better therapeutic range without the need for INR control. Studies for anticoagulation therapy in AF with these new drugs are under way. The authors recommend indicating an interventional occlusion of LAA in AF with strict caution only done by centers with experience with those devices. Only patients with high risk for stroke should be implanted until more data are available.

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